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Original Article

Comparison of the efficacy and safety of warfarin anticoagulation and left atrial appendage transcatheter occlusion in the treatment of non-valvular atrial fibrillation and investigation of ET-1, hs-CRP and PDGFs

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Article Info

Abstract

This study compared the therapeutic effect and safety between warfarin anticoagulation and percutaneous left atrial appendage transcatheter occlusion (PLAATO) in non-valvular atrial fibrillation (NVAF). A total of 110 patients were selected and assigned to Control group (n=55) and Observation group (n=55). The control patients were used warfarin, while the observation patients were performed PLAATO. The coagulation function, stroke and bleeding scores were compared between the two groups at different times. Left ventricular function before therapy and 1 year after therapy and adverse events during follow-up were compared between the two groups. After one month of treatment, CHA2DS2-VASC, HAS-BLED score, serum ET-1 and hs-CRP levels were lower in the PLAATO patients than in warfarin patients, but serum PDGFs levels were higher than patients in the warfarin patients (P < 0.05). One month after treatment, the activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time (TT) of the PLAATO patients was longer than that of the warfarin patients (P < 0.05), but the levels of fibrinogen (FIB) in the PLAATO patients were lower than that of the warfarin patients (P < 0.05). In addition, one year after therapy, the left atrial end-diastolic volume (LAEDV), left atrial end-systolic volume (LAESV) and left atrial inner diameter of the two groups were significantly reduced (P < 0.05). Left atrial appendage (LAA) occlusion can effectively improve the cardiac function and coagulation function of NVAF patients, with lower incidence of bleeding events, stroke events and higher safety.

Keywords: Cardiac function, Clinical effect, Left atrial appendage occlusion, Non-valvular atrial fibrillation, Warfarin.

1. Introduction

Non-valvular atrial fibrillation (NVAF) is a common arrhythmia in clinical patients. It refers to supraventricular tachyarrhythmia that leads to uncoordinated atrial activation and ineffective contraction [1]. NVAF patients often show cardiac function damage, atrial mural thrombus, ventricular rhythm disorder, etc. The disease is an independent risk factor leading to peripheral artery embolism and stroke. It has been confirmed that stroke is the main cause of death or serious disability of NVAF patients [2, 3]. Therefore, it is particularly important to take targeted measures as soon as possible to prevent NVAF stroke events. Warfarin is a classic anticoagulant for the therapy of NVAF, which can prevent stroke in NVAF patients, but it needs to be taken for a long time, and the international standardized ratio (INR) needs to be strictly detected to adjust the dosage [4]. The therapy compliance of patients is low, which can affect the therapy effect, and the application of warfarin to patients with anticoagulation contraindications is limited [5]. Thrombus in NVAF patients mostly occurs in the left atrial appendage (LAA) [6].

LAA occlusion is a new minimally invasive interventional treatment developed in recent years to prevent thrombosis in patients with atrial fibrillation [7]. It closes the traffic between the LAA and the left atrium through minimally invasive intervention using LAA occluder [8], so as to reduce the risk of stroke in NVAF patients, with less trauma and faster recovery [9, 10]. The purpose of this study was to evaluate the safety and efficacy of LAA occlusion and warfarin in the treatment of NVAF.

2. Materials and methods
2.1. General clinical data

A total of 110 NVAF patients admitted to our hospital from June 2019 to June 2021 were selected and divided into the control group (55 cases) and the percutaneous left atrial appendage transcatheter occlusion (PLAATO) patients (55 cases). The warfarin patients were 29 males and 26 females; The average age was 62.88 ± 10.54 years; The course of disease was 5-16 years, with an average of 10.64 ± 2.17 years; The non-valvular ward fibrillation stroke risk score (CHA2DS2-VASC) was 2-5 points, with an average

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of 4.23 ± 0.21 points; The atrial fibrillation bleeding score (HAS-BLED) was 3-5 points, with an average of 3.83 ± 0.44 points [11]. The PLAATO patients contain 27 males and 28 females; The average age was 63.14 ± 11.02 years; The course of disease was $6 \sim 16$ years, with an average of 10.87 ± 2.74 years; Cha2ds2 VASC score was 2-4 points, with an average of 4.25 ± 0.17 points; HAS-BLED score was 3-5 points, with an average of 3.75 ± 0.61 points. There was no significant difference in general data between the two groups (P > 0.05), which was comparable between the two groups. The study was approved by the Ethics Committee of the Second People's Hospital of Lanzhou.

2.1.1. Inclusion criteria

Those who met the NVAF diagnostic criteria in the guidelines and consensus for the prevention and therapy of cardiovascular diseases and were confirmed by ECG examination; CHA2DS2-VASC ≥ 2 points; HAS-BLED ≥ 3 points; Accompanied by palpitations, shortness of breath, dizziness, chest discomfort and other typical symptoms.

2.1.2. Exclusion criteria

Patients with thrombus found in left ventricle and LAA; Patients with abnormal atrial septum; Patients with mitral stenosis and mitral insufficiency; Patients with previous MI; Patients with contraindications of LAA occlusion; Patients with malignant tumor; Allergic to the study drug; Those who have a history of thrombosis in the past. Informed consent was signed by patients and their families.

2.2. Methods

2.2.1. Control group

Took warfarin sodium tablets orally, with 1.5 mg/time, once a day. The INR was rechecked on the 3rd and 7th days of therapy, and the INR was maintained at $2.0 \sim 3.0$. The dose was gradually adjusted according to the test results (slowly adjusted at 0.75 mg each time). During the therapy period, if the INR remained stable, it was detected once a week. If it remained stable for 4 weeks, it was detected once a month. After one year, it was detected once every 2 months.

2.2.2. Observation group

After the venous channel was established, they were given general anesthesia, disinfected, and covered with towels. The shape of the LAA was carefully explored with an esophageal ultrasound probe, and the depth to the tip of the LAA was measured. The appropriate puncture point was selected to perform atrial septal puncture along the femoral vein path. After the puncture was successful, the LAA was imaged by pig's tail catheter and esophageal ultrasound, the shape and size of the LAA were observed, the appropriate watchman occluder was selected, and the occluder was sent to the LAA with its special sheath tube, and slowly deployed. During the operation, the release position deviation was avoided, and the stability of the occluder was tested by pulling test, Release the occluder after confirming that the pass principle (position, anchoring, size, occlusion) is met, pull out the guidewire, sheath and other instruments, apply pressure bandage locally, and closely observe the patient's vital signs during the operation. After operation, patients were given double antiplatelets. The specific method is: clopidogrel bisulfate tablets (com-

pared with aspirin and dipyridamole tablets, the dosage of clopidogrel was 75 mg/time and aspirin was 100 mg/time, both of which were once a day; after that, the treatment scheme was adjusted according to the results of various laboratory tests of the patients. If there was no obvious abnormality, the therapy scheme was adjusted to aspirin long-term maintenance oral treatment, with a dosage of 100 mg/time, once a day. Patients in both groups were followed up for 1 year from the beginning of therapy.

2.3. Observation indicators
2.3.1. Serum endothelin-1 (ET-1), hypersensitive C-reactive protein (hs-CRP) and platelet-derived growth factor (PDGFs)

Fasting venous peripheral blood samples of patients were taken before and after therapy, and the supernatant was taken after centrifugation. Serum ET-1, PDGFs and hs-CRP were detected by ELISA and operated in strict accordance with the kit instructions (Hangzhou Lianke Biotechnology Co., Ltd.). Comparison of the levels of inflammatory factors assessed before and after 1 month of treatment in the two groups.

2.3.2. Four coagulation functions

Before and after therapy, the patients' fasting venous peripheral blood samples were taken, and the levels of four coagulation functions: the activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), and Fibrinogen (FIB) were measured with a full-automatic blood coagulation instrument (Mindray c2000-a). Comparison of coagulation function before and after 1 month of treatment in the two groups.

2.3.3. Left ventricular function

The LAEDV, LAESV and left atrial diameter were measured by Doppler ultrasound analyzer at different time points. Comparison of left ventricular function before and after 1 year of treatment in the two groups.

2.3.4. Adverse events

During the follow-up period, the bleeding and stroke events were recorded and compared between two groups of patients.

2.3.5. Clinical efficacy: Remarkable effect

Clinical symptoms basically disappeared without thrombus. Effective: the clinical symptoms have been improved, and there are very few thrombi, but it does not affect the patient's health. Ineffective: there is no obvious improvement in clinical symptoms and obvious thrombus.

2.3.6. Quality-of-life scores for patients

All patients participating in the study used the SF-36 quality-of-life Scale to assess patients' quality-of-life scores. Left quality-of-life scores before and after 1 month of treatment were compared and assessed in both groups.

2.4. Statistical analysis

SPSS 22.0 statistical and $(x \pm s)$ was used for this study, the difference between two groups was compared via t-test, and the count data was expressed by the rate (%). X^2 test was used for more than 3 groups, and the difference was statistically significant when P < 0.05.

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3. Results

3.1. Comparison of stroke and bleeding scores between the two groups

After 1 month of therapy, CHA2DS2-VASC and HAS-BLED scores in the PLAATO patients and the warfarin patients were both lower than those before treatment (P < 0.05). However, compared with the warfarin patients after therapy, CHA2DS2-VASC and HAS-BLED scores in the PLAATO patients after therapy were significantly decreased (P < 0.05), as shown in Figure 1.

3.2. Comparison of four indexes of coagulation between two groups before and after treatment

One month after therapy, the PT, TT, APTT in the PLAATO patients was longer than patients of the warfarin patients (P < 0.05); The FIB in the PLAATO patients was shorter than patients of the warfarin patients (P < 0.05), as shown in Figure 2.

3.3. Comparison of left ventricular function between two groups

Compared with before treatment, one year after therapy, the LAEDV, left atrial inner diameter and LAESV of the two groups were significantly reduced, Moreover, the PLAATO patients were significantly smaller/shorter (P < 0.05), as shown in Table 1.

3.4. Clinical efficacy analysis between two groups

In the warfarin patients, 18 cases were remarkably effective, 28 cases were effective, and 9 cases were ineffective after treatment; In the PLAATO patients, 30 cases were remarkably effective, 23 cases were effective, and 2 cases were ineffective 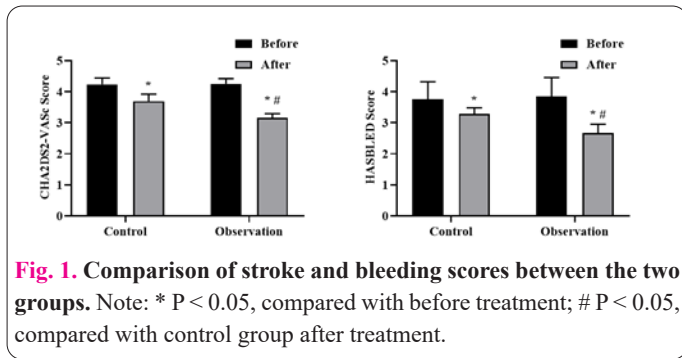after treatment; the total effective rate of the PLAATO patients (96.37%) was higher than that of the warfarin patients (83.64%) (P < 0.05), as shown in Table 2.

3.5. Comparison of serum ET-1, PDGFs and hs-CRP between the two groups

After one month of treatment, the levels of serum ET-1 and hs-CRP in the PLAATO patients were lower than those in the warfarin patients, and the levels of serum PDGFs were higher than those in the warfarin patients. The difference was statistically significant (P < 0.05), as shown in Figure 3.
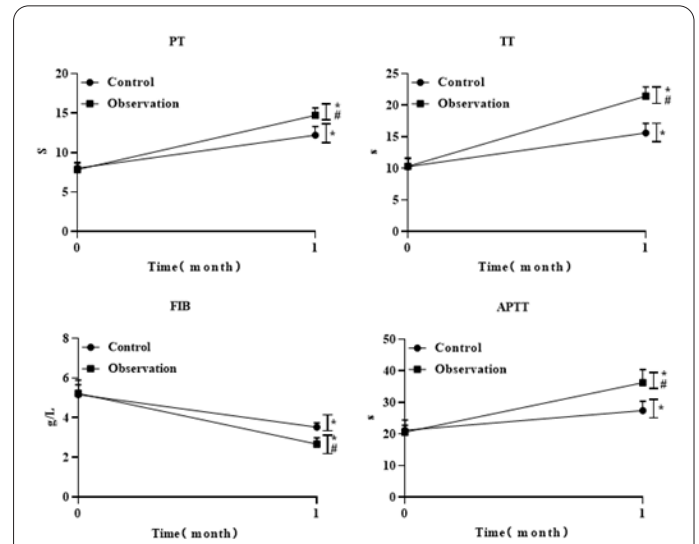

Fig. 2. Comparison of four indexes of coagulation between two groups. Note: * P < 0.05, compared with before treatment; # P < 0.05, compared with control group after treatment.

Fig. 1. Comparison of stroke and bleeding scores between the two groups. Note: * P < 0.05, compared with before treatment; # P < 0.05, compared with control group after treatment.
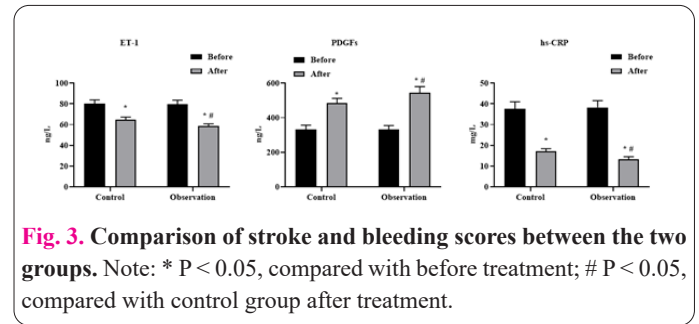

Fig. 3. Comparison of stroke and bleeding scores between the two groups. Note: * P < 0.05, compared with before treatment; # P < 0.05, compared with control group after treatment.

Table 1. Comparison of left ventricular function between two groups.

| Groups | N | LAEDV (ml) | | LAESV (ml) | | LA (mm) | |
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	55	88.06±11.65	85.83±10.03*	64.15±10.84	61.99±9.89*	46.89±4.68	44.77±1.88*
Control group	55	88.31±10.18	80.06±10.59*	64.38±11.02	53.06±11.69*	47.02±4.38	42.26±1.09*
t		0.170	4.158	0.156	6.128	0.213	12.155
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

* P < 0.05, compared with before treatment.

Table 2. Clinical efficacy analysis between two groups.

Groups	Remarkable effective	Effective	Ineffective	Effective rate
Control group	18 (32.73)	28 (50.91)	9 (16.36)	83.64
Observation group	30 (54.55)	23 (41.82)	2 (3.63)	96.37
t				4.731
P				<0.05

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Table 3. Comparison of adverse incidence and complications between the two groups.

Groups	N	Adverse reactions				Complication		
		Bleeding	Rash	Gastrointestinal reaction	Incidence (%)	Stroke	Arterial embolism	Incidence (%)
Observation group	55	2 (3.64)	1 (1.82)	4 (7.27)	12.73	1 (1.82)	2 (3.64)	5.45
Control group	55	3 (5.45)	3 (5.45)	6 (10.9)	21.82	3 (5.45)	5 (9.09)	14.55
t					4.578			6.018
P					<0.05			<0.05

3.6. Comparison of adverse reactions and complications between the two groups

Within 1 month after therapy, the total adverse incidence and complications were lower in observation patients than in the control patients (P < 0.05), as shown in Table 3.

3.7. Comparison of the quality-of-life scores between the two groups

Before treatment, there was no significant difference in the quality-of-life scores between the two groups (P>0.05). After one month of treatment, the quality-of-life scores of patients in the observation group were significantly higher than those in the control group, and the differences between the two groups were statistically different (P < 0.05, Table 4).

4. Discussion

NVAF is atrial fibrillation other than heart valvular disease, which is clinically characterized by rapid and disordered atrial beats. The main harm is to affect the output of the heart. When atrial fibrillation occurs, the ventricle cannot be filled without effective contraction. Due to the lack of atrial contraction, blood accumulates in the right atrium, which is easy to cause thrombosis and increases the risk of stroke [12]. Studies have reported that NVAF not only causes serious complications such as embolism and stroke but also has a high mortality rate. With the increase in patients' age, the incidence rate of NVAF gradually increases [13]. Studies have reported that NVAF not only causes serious complications such as embolism and stroke but also has a high mortality rate. With the increase in patients' age, the incidence rate of NVAF gradually increases.

The left auricle is the main site of thrombus formation in atrial fibrillation [14], and more than 90% of patients with non-valvular atrial fibrillation have thrombus originating from the left auricle, and closure of the left auricle is one of the effective ways to prevent thromboembolism in patients with non-valvular atrial fibrillation. There are two interventional methods of left auricular closure that are most clinically established today. The first is the implantation of an occlusion device to occlude the left heart ear. At present, the main devices for left-ear occlusion are the WATCHMAN plug and the Amplatzer Cardiac Plug (ACP) plug. Early studies suggest124 that the WATCHMAN device is not at a disadvantage compared with warfarin for the composite endpoint events of thromboembolism and cardiovascular death, with approximately 1 in 5 patients experiencing early adverse events, such as pericardial hemorrhage. Follow-up registry studies have confirmed that implantation of the WATCHMAN device does not significantly increase the incidence of adverse events such as bleeding in patients who cannot receive warfarin anticoagulation. The second type is ligation of

Table 4. Comparison of the quality-of-life scores between the two groups.

Groups	N	SF-36 scores	
		Before treatment	After treatment
Observation group	55	72.42±7.16	94.33±6.19
Control group	55	73.61±6.78	83.27±7.51
t		0.89	16.35
P		>0.05	<0.001

the left heart ear using a catcher, such as the LARIAT device. Some studies have shown that the LARIAT device is 97% effective in closing the left auricular cavity and has a good safety profile. Left-ear occlusion has been shown to be effective in reducing thromboembolic events in patients with non-valvular AF, particularly in patients with non-valvular AF who have contraindications to anticoagulants.

When warfarin method is applied to patients with atrial fibrillation, it can timely inhibit the generation of coagulation factors and thromboembolism, effectively prevent the expansion and spread of thrombus, and effectively control the shedding of thrombus [15]. However, the therapeutic window of warfarin is narrow, and its anticoagulant effect will be affected by many factors such as food and drugs. It is necessary to dynamically monitor the coagulation function and implement individualized administration by monitoring the international standardized ratio (INR) [16]. As a permanent implant device, the LAA occluder can reduce or prevent cardiogenic cerebral embolism by closing the LAA. In recent years, the efficacy and safety of PLAATO in preventing NVAF stroke have been confirmed by a number of randomized controlled and registered studies. Clinical studies on the prevention of embolism events by LAA intervention have emerged in an endless stream. Surgical intervention of LAA and percutaneous LAA occlusion have also been frequently applied to the clinic by many domestic centers [17, 18]. Evidence-based studies have preliminarily shown that compared with the warfarin treatment group alone, the probability of hemorrhagic stroke, disabling stroke and cardiovascular death (including death from unknown causes) in the occluder implantation group is significantly lower, which is similar to those reported [13, 19], suggesting that treatment with left auricular occlusion in patients with NVAF is effective in reducing the occurrence of bleeding events and is safe and feasible. It may be related to the fact that in recent years, with the accumulation of operator's operational experience, the complication rate related to left ear occlusion has gradually decreased, the safety has gradually improved, and the risk of the procedure is lower. Therefore, compared with the warfarin treatment group, the embolization prevention effect, safety and effectiveness of LAA after effective intervention are significantly prominent.

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Serum ET-1 and hs-CRP levels in the PLAATO patients were lower than those in the warfarin patients, and serum PDGFs levels were higher than those in the warfarin patients. CHA2DS2-VASC score can reflect the risk of thrombus in patients with atrial fibrillation. The higher the score, the higher the risk [19]. ET-1 is a cytokine that promotes vasoconstriction and inflammatory response. The elevation of ET-1 causes vasoconstriction, slows blood flow, and easily leads to thrombosis [20]. The hs-CRP is an indicator commonly used in clinics to detect the inflammatory level of patients. When the body receives inflammatory stimulation, the level of hs-CRP rises. PDGFs participate in the regulation of many physiological times and diseases of the body and play important roles in the regulation of formation and function of blood vessels [21]. Another study pointed out that LAA and warfarin have the same effect on preventing thrombus, which indicates that both drugs can play better roles in treatment and prevention. LAA has a better effect on improving vascular function than warfarin [22]. The results of this study showed that after one month of treatment, the coagulation function of both groups of patients was improved. It indicated that both drugs had good anticoagulant efficacy, which was partially consistent with the existing studies [23].

LAEDV, LAESV, and left ventricular inner diameter are important indicators for evaluating the left ventricular systolic function of patients. If the volume and inner diameter are too large or reduced, it indicates that the patient's cardiac systolic capacity is decreased and the ECG activity is abnormal, leading to arrhythmia. Patients with atrial fibrillation are prone to lead to the reconstruction of the left atrium, which in turn leads to changes in the cardiac structure of patients. It is easy to lead to atrial fibrillation again after patients turn to sinus rhythm [14]. After the closure of the LAA, the volume regulation effect of the body will be reduced, thus making the volume smaller. The change in hemodynamics after the closure can cause the blood flow speed of the left atrium to become faster, thereby reducing the incidence of thrombosis and improving cardiac function [24]. The results of this study showed that after one year of treatment, the LAEDV and LAESV of the observation group were significantly smaller than those of the warfarin patients, and the left atrial inner diameter was significantly shorter than that of warfarin patients, suggesting that the LAA occlusion can improve the cardiac function of NVAF patients more effectively. This is similar to the results of related studies [25, 26]; it is clear that PLAATO has comparable advantages to warfarin in preventing embolism, cardiovascular events or stroke in NVAF patients.

5. Conclusion
To sum up, compared with warfarin, PLAATO can effectively improve the cardiac function and coagulation function of NVAF patients, with lower incidence of bleeding events, stroke events and higher safety. This study is worthy of further clinical research and application.

Consent for publications
All authors approve the final manuscript for publication.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Second People's Hospital of Lanzhou. Informed consent was signed by patients and their families.

Data availability statement
The original data used to support the findings of this study are available from the corresponding author upon request.

Conflict of interest
The author reported that there is no conflict of interest.

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